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Novel Syndromes Associated with JC Virus Infection of Neurons and Meningeal Cells: no longer a gray area

Dhanashri P. Miskin and **Igor J. Koralnik**

Division of NeuroImmunology and Center for Virology and Vaccine Research, Department of Neurology and Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Purpose of review—The availability of a growing number of immunomodulatory medications over the past few years has been associated with various JC Virus (JCV) associated brain syndromes in patients with autoimmune diseases, including multiple sclerosis, Crohn's disease and psoriasis which had not been previously recognized as predisposing factors for progressive multifocal leukoencephalopathy (PML). This review covers the three novel syndromes discovered in the last decade which are caused by JCV infection of neurons and meningeal cells.

Recent findings—For more than 30 years, JCV was thought to exclusively infect oligodendrocytes and astrocytes in the white matter of the brain of immunosuppressed individuals. We now recognize that JCV-infected glial cells are frequently located at the gray-white matter junction or exclusively within the gray matter causing demyelination in the cortex. Mutations in JCV can trigger a change in tropism leading to involvement of other cell types, such as neurons and meningeal cells, causing clinically distinct entities. These new features of JCV infection provide challenges for clinicians taking care of affected patients and investigators studying the biology of this polyomavirus, its pathogenesis, and tropism.

Summary—We hope that increasing awareness of these syndromes will lead to early diagnosis, and pave the way for new avenues of research to better understand all aspects of JCV pathogenesis and develop efficient therapies for our patients. However, we need to remain vigilant and open to the possibility that additional JC variants or yet unknown polyomaviruses may be associated with neurological diseases as well.

Keywords

Progressive multifocal leukoencephalopathy; JC virus granule cell neuronopathy; JC virus encephalopathy; JC virus meningitis

Correspondence to Igor J. Koralnik, MD, Chief, Division of NeuroImmunology and Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, E/CLS - 1005, 330 Brookline Avenue, Boston, MA 02215, USA Tel: +1 617 735 4460; fax: +1 617 732 4527; ikoralni@bidmc.harvard.edu.

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Introduction

JCV is a ubiquitous human polyomavirus that infects 50% to 86% of healthy adults without causing any disease. The virus remains quiescent in the kidney and lymphoid organs and may also remain latent in the brain [1]. In immunosuppressed individuals, including those with acquired immunodeficiency syndrome (AIDS), hematological malignancies, transplant recipients and patients with autoimmune diseases treated with immunomodulatory medications, JCV may reactivate and cause a productive and lytic infection of oligodendrocytes and astrocytes, leading to the often fatal demyelinating disease of the central nervous system (CNS) – PML.

With the growing amount of knowledge gathered since this disease was originally named 43 years ago, we have come to realize that “progressive multifocal leukoencephalopathy” has become somewhat of a misnomer. Indeed, we now understand that PML is not always progressive, may affect a single area of the brain, can involve both gray and white matter, and is sometimes associated with intense inflammation [2]. PML was initially characterized by multifocal areas of demyelination containing JCV infected oligodendrocytes, as well as reactive gliosis with enlarged, bizarre astrocytes infected by JCV. While PML lesions are predominantly localized in the subcortical white matter [3], lesions have also been found within gray matter structures.

For the first 32 years since its discovery in 1971 [4], JC virus was thought to exclusively infect oligodendrocytes and astrocytes in the brain white matter, while neurons were deemed not to be susceptible to infection [5]. We have described 3 novel syndromes caused by infection of neurons and meningeal cells. In 2003, we demonstrated productive infection of cerebellar granule cell neurons by JCV [6], and in 2005, JCV granule cell neuronopathy (JCV GCN) was characterized [7]. JCV GCN is caused by a JCV variant harboring a small deletion in the VP1 capsid protein, with specific tropism for cerebellar granule cell neurons. This infection results in cerebellar atrophy and associated dysarthria, appendicular, and gait ataxia [6-8]. In 2009, we reported a gray matter disease, JCV encephalopathy (JCVE), in one human immunodeficiency virus (HIV)-negative patient with lung cancer [9]. JCVE was found to be caused by a productive infection of cortical pyramidal neurons. Finally, in 2014, we observed a fatal case of JCV meningitis (JCVM) in an HIV-negative patient who had an extremely high CSF JC viral load and productive JCV infection of leptomeningeal cells [10]. In this review, we will discuss these syndromes in detail and how their discoveries have expanded our understanding of the pathogenesis of JCV in the CNS.

JCV Granule Cell Neuronopathy (JCV GCN)

Demyelination of the cerebellum white matter is well described in patients with PML. However, occasional focal cell loss in the granule cell layer of the cerebellum has also been reported in early cases [11, 12]. In 2000, Tagliati et al reported a syndrome of unexplained degeneration of the cerebellar granule cell layer occurring in association with HIV infection [13]. In 2003, we observed a patient with AIDS who developed PML in the subcortical white matter of both frontal lobes, and an unexplained cerebellar syndrome and cerebellar atrophy. A post mortem exam showed that in addition to classic PML lesions in the cerebral

hemispheric white matter, the patient sustained a productive infection of cerebellar granule cell neurons by JCV in the absence of MRI or histologic evidence of demyelination in the cerebellum [6]. In 2005, we described isolated cerebellar atrophy caused by destruction of cerebellar granule cell neurons by JCV and named this syndrome, distinct from PML, JCV granule cell neuronopathy (JCV GCN) [14]. Since then, this condition has been reported independently throughout the world, mostly in HIV infected patients [6, 7, 15-22], but also in patients with CD40 ligand deficiency [23], sarcoidosis [12, 24], and more recently, in one patient with non-Hodgkin lymphoma treated with rituximab [25] and two Multiple Sclerosis patients treated with natalizumab [26-28].

In JCV GCN, JC virus causes productive and lytic infection of granule cell neurons in the granule cell layer of the cerebellum, but spares Purkinje cells [29]. A histologic survey of archival PML samples indicated that infection of granule cell neurons is in fact frequent and may be found in up to half of patients with PML, irrespective of whether they have concomitant demyelinating lesions of PML in the nearby cerebellar white matter. Infection of GCN was also found in 1/35 HIV-positive control samples without PML, indicating that neurons may also be the initial site of infection in the brain [30]. HIV-infected JCV GCN patients treated with cART have a median survival of at least 1.8 years as opposed to untreated patients whose median survival was only months [20].

Patients develop a subacute cerebellar syndrome characterized by truncal and appendicular ataxia, dysdiadochokinesia, dysmetria on finger to nose and heel to shin testing, and dysarthria. MRI typically shows cerebellar atrophy suggestive of neurodegeneration (Figure 1). However, additional white matter changes in the cerebellum and brainstem, particularly in the middle cerebellar peduncles and the pons, can frequently be seen [22]. A definitive diagnosis is established by PCR detection of JCV DNA in CSF or by cerebellar biopsy showing infection of granule cell neurons by JCV and immunohistochemistry (IHC) by using a neuronal marker, such as NeuN or MAP-2, together with anti-T Ag antibody v-300. The infected granule cell neurons have a hypochromatic, enlarged nucleus, and can be seen on the edges of areas of focal cell loss [7].

Molecular analyses of brain and cerebrospinal fluid (CSF) samples from 6 of these JCV GCN cases showed small deletions in the C-terminal portion of the VP1 gene [8, 21, 26]. This area is responsible for linking the 72 pentamers of the VP1 protein that form the viral capsid, and is not directly exposed to the virion surface [2]. Therefore, these mutations are unlikely to cause a direct change in receptor binding but may rather affect post-entry events that may favor replication and assembly in granule cell neurons [21]. Mutated JCV strains can be found concomitant to undeleted strains in CSF and blood of PML patients, suggesting that the JCV variant that causes GCN may arise from outside the CNS. The JCV regulatory region (RR), which is required for viral expression and DNA replication, contains numerous binding sites for cellular proteins. Whereas the JCV-coding region is extremely conserved, the hypervariable non-coding RR has been associated with neurotropism and neurovirulence. We hypothesized that the RR for the JCV GCN1 variant isolated from the cerebellum of our index patient should have a uniquely different sequence allowing its growth in granule cell neurons. However, we found this to not be the case as the RR of the

JCV GCN1 mutant had the same tandem-repeat pattern seen in classic PML patients suggesting that the specific tropism for neuronal cells is likely unrelated to its RR. [31, 32].

JCV Encephalopathy (JCVE)

It has long been known that demyelinating lesions of PML can extend into the cerebral gray matter [3, 33, 34], and that some neurons may contain JCV DNA, T Ag, and VP1 protein [35]. However, in 2009, we observed an HIV-negative patient who developed global cognitive decline, seizures, and aphasia. The clinical presentation differed from both classic PML and JCV GCN. Brain lesions were initially restricted to the hemispheric gray matter on MRI (Figure 2), which is the opposite of typical white matter lesions of PML. However, JCV was detected in the cortical gray matter and CSF [2]. We named this novel syndrome JCV encephalopathy (JCVE). Since this patient had a weak anti–JCV immunoglobulin M response four months after the start of her disease, JCVE may have been caused by a primary infection.

In JCVE, JCV infection predominantly involves cerebral pyramidal neurons and astrocytes in the cortical gray matter and gray-white junction. The presence of viral proteins in the nuclei, cytoplasm and axons of neurons suggests that JC virus may spread in the brain by migrating through axons of infected neurons [9]. More neurons were found to contain JCV T Ag, a regulatory protein expressed early in the viral life cycle, than JCV VP1 capsid protein which is produced at the time of viral assembly, suggesting the JCV infection of cortical pyramidal neurons may be abortive in those cells. We performed PCR amplification of the C terminus of the VP1 gene and sequencing to determine whether the same VP1 capsid deletion associated with JCV GCN was responsible for tropism of cortical pyramidal neurons. Interestingly, the VP1 gene was intact. However, isolation and sequencing of the JCV DNA present in the brain of this patient identified a virus with an archetype-like RR usually found in urine and kidney isolates of the virus, and a 143 base pair deletion in the agnoprotein gene [36]. The deleted agnogene encodes a 10 amino acid truncated peptide and is responsible for the majority of the JCV Cortical Pyramidal Neuron (JCV_{CPN}) phenotype. Further analysis found that multiple forms of JCV_{CPN} were present in the brain of this patient, and that these strains co-existed with a virus containing a full length agnogene. Compared to JCV prototype Mad-1 which readily infects glial cells, JCV_{CPN} was not able to maintain a persistent infection in vitro, although it was capable of replicating in multiple cell lines. Experiments with chimeric viruses between JCV_{CPN} and $JCV_{Mad\text{-}1}$ indicated that the agnogene deletion, rather than the kidney-type regulatory region, was the cause of this particular phenotype [37]. Further experiments demonstrated that the deletion of nucleotides 376-396 in the agnogene results in decreased levels of virus DNA replication and a lack of expression of the VP1 capsid protein [38]. Although this observation stems from a single case, these data suggest that the agnogene deletion of this particular JCV strain allowed for the virus to infect and propagate into cortical pyramidal neurons. Further studies are needed to determine whether this particular JC deletion variant actually plays a role in cortical pyramidal neuron infection in other cases.

JC Virus Meningitis (JCVM)

Although JCV is not routinely tested for in the CSF of patients with meningitis or encephalitis, several studies have documented JCV as the only pathogen present in the CSF of patients with typical meningeal signs and symptoms, such as neck stiffness and diplopia. Whether these cases result from JCV primary infection or reactivation is unclear. The exact incidence of JCV meningitis remains unknown as JCV PCR is not routinely performed in the CSF of patients with aseptic meningitis with an unremarkable MRI. In a large CSF study of patients with suspected meningitis or encephalitis, PCR showed that two HIV-negative individuals with no parenchymal brain lesions had detectable JCV DNA in their CSF. One of these patients ultimately died of cerebral lymphoma and, therefore, probably had an undocumented underlying immune suppression [39]. There are only 3 case reports of JCV meningitis (JCVM) to date. The first involved an immunocompetent girl who was diagnosed based on increasing JCV antibodies in the serum [40]. The second was a 38-year-old woman with systemic lupus erythematosus who presented with fevers, headaches, and altered mental status and was found to have JCV DNA in the CSF. She had no white matter lesions on MRI and her symptoms spontaneously resolved [41]. Recently we described a fatal case of JCVM in an HIV-seronegative patient who presented with a subacute meningoencephalitis and the classic triad of cognitive impairment, gait dysfunction, and urinary incontinence consistent with secondary normal pressure hydrocephalus. MRI also revealed FLAIR hyperintensity within the sulci but no white matter lesions, cerebellar atrophy, or cortical abnormalities (Figure 3). CSF JC viral load was extremely high, up to 48 million copies/ml. Post mortem exam showed productive JCV Infection of leptomeningeal and choroid plexus cells. Molecular analyses from the CSF JCV strain demonstrated an archetype-like RR, but no VP1 gene or agnogene mutations such as those found in cases of JCV GCN of JCVE [10]. Further studies on the role of JCV in aseptic meningitis and idiopathic hydrocephalus are warranted.

Conclusion

It is now firmly established that JCV infection is not restricted to the CNS white matter. JCV also causes demyelination of cortical gray matter, as well as several types of gray matter disease caused by neuronal infection. Furthermore, JCV has also come out of the “gray area” by showing its ability to infect meningeal and choroid plexus cells. JCVM, JCVE, JCV GCN, and PML may occur separately or co-exist on a continuum as the virus mutates and spreads from one location to another (Figure 4). Of note, seizures, which are considered to be of cortical origin, occur in up to one-third of PML patients and have been associated with lesions located at the gray-white junction [34, 42]. Therefore, the gray matter involvement by JCV itself may provide a more direct mechanism by which this virus causes frequent seizures. In fact, seizures were associated with JCV-associated cortical demyelination, astrogliosis and infiltrates by phagocytic macrophages in a recent PML study [34].

Interestingly, infection of neurons by polyomaviruses is not restricted to humans. The JCV-related simian virus 40 (SV40) can causes a fulminant and productive infection of cortical pyramidal neurons in simian-human immunodeficiency virus (SHIV)-immunosuppressed

rhesus monkeys [43]. A retrospective analysis showed SV40 infection of neurons or meningeal cells in two thirds of immunosuppressed monkeys who developed a PML-like disease [44].

Due to the increasing number of patients treated with new generations of immunosuppressive drugs such as monoclonal antibodies, inhibitors of leukocyte migration, and fumarates—used for the treatment of multiple sclerosis, psoriasis, hematological malignancies, Crohn's disease, and rheumatic diseases—a substantial increase of patients with JCV-associated brain diseases could be on the horizon [45]. Our hope is that increasing awareness of these novel syndromes will lead to early diagnosis, and pave the way for new avenues of research to better understand all aspects of JCV pathogenesis and develop efficient therapies for our patients. However, we need to remain vigilant and open to the possibility that other JCV variants or perhaps, yet unknown polyomaviruses, may causes additional shades of gray matter damage in the CNS, that are yet to be discovered.

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Key points

- PML is not always progressive, multifocal, or restricted to the white matter of the brain.
- Three novel syndromes associated with JC Virus (JCV) have been characterized in the last decade: JCV GCN, JCVE, and JCVM, expanding the pathogenesis of JCV and opening new areas of investigations.
- JCV variant strains, co-infection with wild-type and deleted strains, and perhaps genetic predisposition all determine astroglial, neuronal, or meningeal tropism.

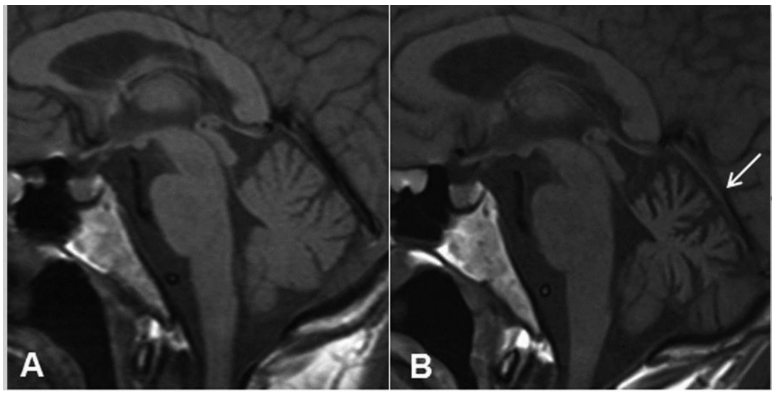

Figure 1. JC Virus Granule Cell Neuronopathy (JCV GCN)

MRI demonstrates progressive cerebellar atrophy without intra-parenchymal lesions. (A) Pre-contrast T1 sagittal image illustrating the size of the cerebellum at symptoms onset. (B) Pre-contrast T1 sagittal image done 4 months later and a week after positive CSF JC Virus PCR shows marked cerebellar atrophy (arrow).

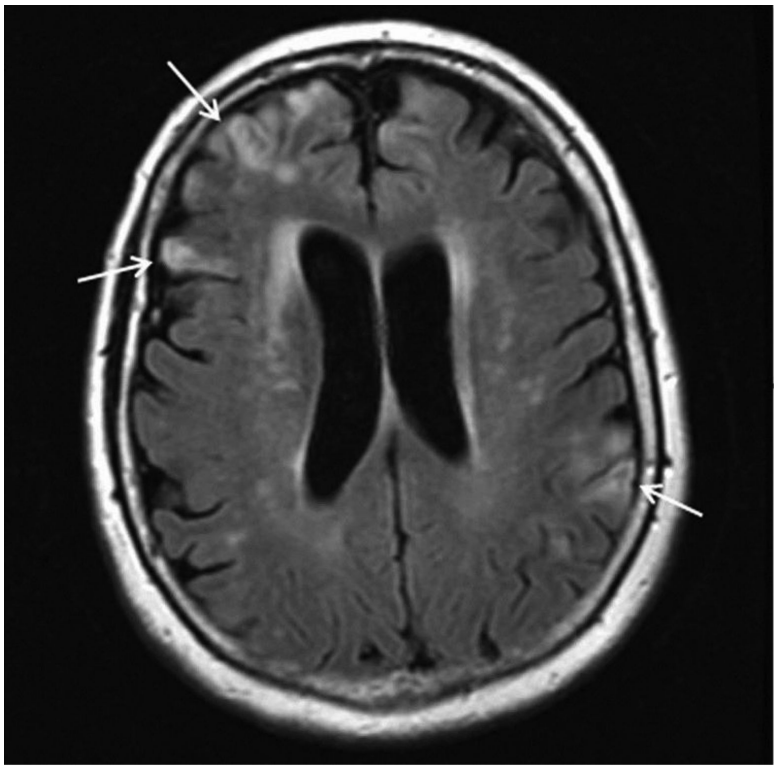

Figure 2. JC Virus Encephalopathy (JCVE)

MRI demonstrates multiple cortical lesions with hyperintense signal on fluid-attenuated inversion recovery sequence in the cerebral hemispheres bilaterally (arrows).

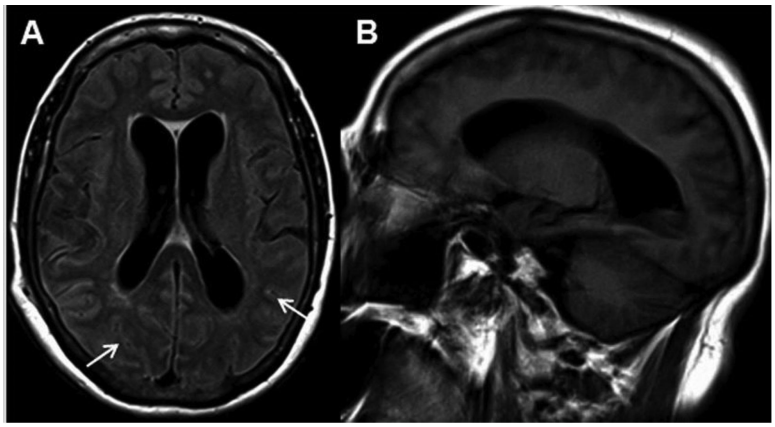

Figure 3. JC Virus Meningitis (JCVM)

MRI demonstrates hydrocephalus, abnormal signal in subarachnoid space, and no parenchymal brain lesions. (A) Axial fluid-attenuated inversion recovery sequence shows enlarged ventricles and abnormal hyperintensity in the subarachnoid space, within the sulci of the cerebral hemispheres (arrows). (B) A sagittal T1-weighted sequence demonstrates significant enlargement of the lateral ventricle.

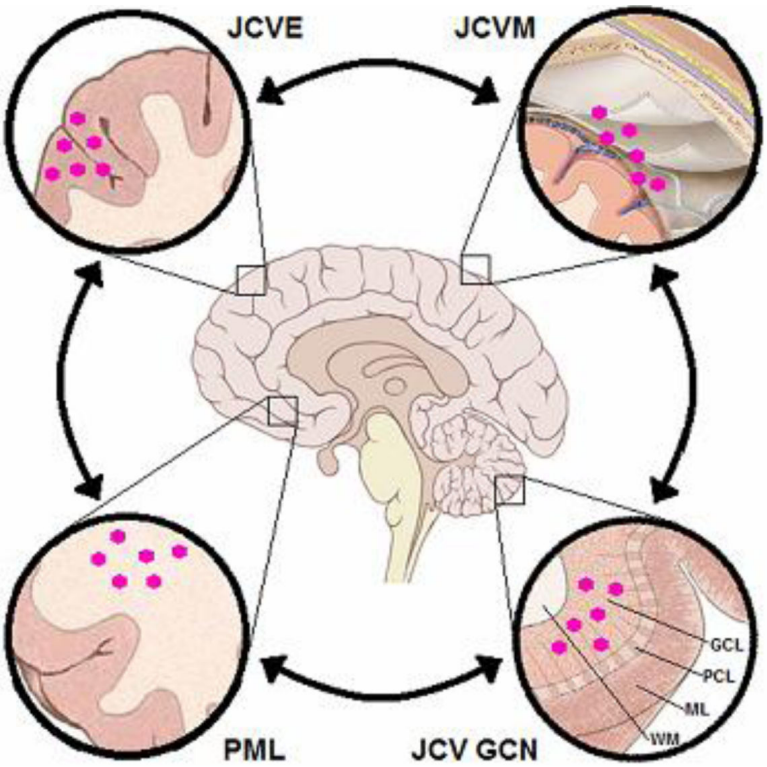

Figure 4. Continuum of CNS syndromes caused by JC Virus (JCV)

The arrows indicate that more than one syndrome may coexist. PML = progressive multifocal leukoencephalopathy; JCVE = JC Virus Encephalopathy; JCVM = JC Virus Meningitis; JCV GCN = JC Virus Granule Cell Neuronopathy; GCL = Granule Cell Layer; PCL = Purkinje Cell Layer; ML = Molecular layer; WM = white matter; ⬢ = JC virion